#17

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of	Group Art Unit: 1616
STEVEN C. QUAY	Examiner: G. Hollinden
Appln. No. 08/896,821	**FOURTH DECLARATION OF PAMELA HILPERT, M.D., Ph.D.**
Filed: July 18, 1997	
For: PERSISTENT GASEOUS BUBBLES AS ULTRASOUND CONTRAST MEDIA	2001 Ferry Building San Francisco, CA 94111 (415) 433-4150

I, Pamela Hilpert, M.D., Ph.D., declare under the penalty of perjury that the following is true and correct:

1. I previously executed sworn statements entitled DECLARATION OF PAMELA HILPERT dated January 9, 1998 (hereinafter "FIRST HILPERT DECLARATION") in two separate, but related, Patent Office proceedings (Reexamination Nos. 90/004,656 and 90/004,657). I understand that a copy of the FIRST HILPERT DECLARATION filed in Reexamination No. 90/004,657 on U.S. Patent No. 5,573,751 is being concurrently submitted with this declaration. I hereby affirm all of the statements made in the FIRST HILPERT DECLARATION for the purposes of the subject proceeding.

2. I previously executed a sworn statement entitled SECOND DECLARATION OF PAMELA HILPERT dated

July 31, 1998 (hereinafter "SECOND HILPERT DECLARATION") in Appln. No. 08/466,104. I understand that a copy of the SECOND HILPERT DECLARATION is being concurrently submitted with this declaration. I hereby affirm all of the statements made in the SECOND HILPERT DECLARATION.

3. My relevant qualifications and background are detailed in my FIRST HILPERT DECLARATION and remain unchanged since that time.

4. In addition to the materials listed as having been reviewed in my FIRST HILPERT DECLARATION, I have reviewed the following document in preparation for providing this declaration: U.S. patent application serial number 08/896,821, i.e., the current application in which this declaration is made (hereinafter "the Quay application" or "the application").

5. As I stated in my FIRST HILPERT DECLARATION and my SECOND HILPERT DECLARATION, I am the author of a paper entitled "Contrast Agents in Diagnostic Ultrasound," which was published as Chapter 3 of Volume 1 of a multi-volume text entitled, Diagnostic Ultrasound. A true and correct copy of that chapter, as published in 1991, is attached hereto as Exhibit 1. Exhibit 1 is referred to in the rest of this declaration as the "Hilpert Chapter." Relevant details regarding the preparation and subject matter of the Hilpert Chapter are provided in my SECOND HILPERT DECLARATION.

6. Based on my personal experience with the state of the art of ultrasound contrast up to and including 1991, and my review of the Quay application, I conclude that one skilled in the art of developing ultrasound contrast agents in the 1991 time frame would have readily understood from the text of the Quay application that an enhancing agent of microbubbles of gases such as perfluoropropane, perfluorobutane and perfluoropentane used for enhancing the contrast in an ultrasound image were part of the invention disclosed. I also conclude that such enhancing agents further including aqueous solutions or suspensions of protein, liposomes, microspheres, or crystals in a saccharide diluent were also part of the disclosed invention. I reach this conclusion based on the evidence and reasoning set forth in my SECOND HILPERT DECLARATION and on the following:

(1) The invention of the Quay application is described in the "Brief Description of the Invention" section of the application (pages 20-21 of the specification) as a method whereby "one skilled in the art may specially select particular gases based on their physical and chemical properties for use in ultrasound imaging. These gases can be used to produce the contrast-enhancing media that is also the subject matter of this invention." This section goes on to briefly discuss the gas selection method. The section concludes with the statement "[u]sing

existing techniques, substantially improved contrast-enhancing media may then be produced and used to improve the quality and usefulness of ultrasound imaging." My understanding of these statements is that the Applicant considered his invention to include (a) selecting particular gases for use in ultrasound contrast imaging based on the disclosed method, and (b) incorporating the selected gas into a contrast agent using any otherwise then known techniques to produce improved contrast-enhancing media, i.e., an improved contrast agent. One skilled in the art would reasonably come to the same understanding.

(2) The inventive method of selecting gases is more particularly described in the "Detailed Description of the Invention" section of the application (p. 21 et seq.) and particularly involves the determination of the Q value for candidate gases. As set forth on page 24 of the specification, the Q value for a particular gas X describes the stability of microbubbles of gas X in a given liquid and can further "be used to determine the utility of gas X as an ultrasound contrast-enhancing agent as compared to air." The application further discloses that for a gas having a Q value greater than one, microbubbles formed of the gas will survive in solution longer than air bubbles. (p.25). At pages 34-35, the application states that "[t]he higher the Q-value, the more promising is the particular gas." These

statements reasonably convey to one skilled in the art that the inventive method includes selecting gases for use as contrast agents on the basis of their relative calculated Q values.

(3) At pages 28-29, Table II of the application shows calculated Q values for a number of gases. Of the listed gases, perfluoropentane (dodecafluoropentane) and perfluorobutane (decafluorobutane) have the highest and second highest calculated Q values, (Q = 207,437 for perfluoropentane and Q = 13,514 for perfluorobutane, respectively). Perfluoropropane (octafluoropropane) has the fifth highest calculated Q value (Q = 1299). These calculations together with the prior expressed desire to choose gases with high Q values, convey to one skilled in the art that the applicant was in possession of the particular gases perfluoropropane, perfluorobutane and perfluoropentane for use as contrast agents.

(4) The Quay application discloses a number of then existing techniques for making ultrasound contrast media. The descriptions of these techniques particularly appears in the Quay application in the "BACKGROUND" section under the headings "Techniques for Measuring Ultrasound Contrast-Enhancement Phenomena" and "Materials Presently Used as Contrast-Enhancing Agents" (application pages 6-20). This review of the existing contrast agents in development is consistent with the descriptions in the Hilpert

Chapter and is an accurate reflection of the state of the art in 1991.

(5) Among the known techniques described in the application is the making of solutions in which microbubbles are stabilized by human protein. This description appears in the Quay application under the heading: "Materials Presently Used as Contrast Enhancing Agents", and the subheading "Microbubbles" (application pages 16-17).

(6) As explained in the Hilpert Chapter, those developing contrast agents in the years leading up to 1991 were familiar with protein stabilized microbubbles of air. By way of example, in the section entitled "ENCAPSULATED GAS BUBBLES" at page 33 of the Hilpert Chapter, I reported that "(s)onication of 5% human serum albumin produces a gas-filled microbubble that is small (3 to 5 μm) and stable enough to allow free passage through the pulmonary circulation.

(7) The Quay application also describes the known technique of using phospholipid-based liposomes containing a gas or gas precursor as a contrast enhancing agent. This description appears in the Quay application under the heading: "Materials Presently Used as Contrast Enhancing Agents", and the subheading "Liquids and Emulsions" (application pages 15-16). As described, the incorporation of gas or gas precursors into the liposome core increases the life span of the gas.

(8) The Quay application also describes the known technique of using a suspension of encapsulated air-filled microspheres for contrast enhancement. Particular air-filled microspheres discussed in the application include those sold under the tradename Albunex (Molecular Biosystems, San Diego, California). This description appears in the Quay application under the heading: "Techniques for Measuring Ultrasound Contrast-Enhancing Phenomena", and the subheading "Beam Attenuation" (application page 13).

(9) As explained in the Hilpert Chapter, those developing contrast agents in the years leading up to 1991 were familiar with encapsulated air-filled microspheres. In the section entitled "ENCAPSULATED GAS BUBBLES" at pages 33 through 37, I reported extensively on studies performed with the Albunex product (encapsulated human protein microspheres).

(10) The Quay application also describes a contrast enhancing agent in powder form that forms a suspension of crystals when mixed with a saccharide diluent, sold under the tradename SHU-454 (Schering, A.G., West Berlin, Germany). The application states that crystals of this agent were suspected to trap microbubbles to provide enhanced contrast. This description appears in the Quay application under the heading: "Materials Presently Used as Contrast Enhancing Agents", and the subheading "Solids and Particles" (application page 15).

(11) As explained in the Hilpert Chapter, those developing contrast agents in the years leading up to 1991 were familiar with the SHU-454 contrast enhancing agent product. In the Hilpert Chapter in the section entitled "FREE GAS MICROBUBBLES" at pages 33 through 32, I reported extensively on studies performed with the SHU-454 product. I further described the product as a "powdered polysaccharide that, when mixed with a diluent, forms a crystalloid-microbubble suspension." I also reported that the mechanism of increased echogenicity was currently unknown, but that the trapping of gas bubbles was one theory postulated.

(12) It is my opinion that the application alone is sufficient to convey to one skilled in the art that the applicant was in possession of contrast enhancing agents of microbubbles of the above specific gases, including such contrast enhancing agents further comprising solutions or suspensions of proteins, liposomes, microspheres or crystals in a saccharide diluent. The application clearly conveys that the Applicant considered his invention to include incorporating a gas selected according to the disclosed method (including the particularly selected gases perfluoropropane, perfluorobutane and perfluoropentane) into a contrast agent using otherwise then known existing techniques. The reference in the "Brief Description of the Invention" to "existing techniques" would reasonably be read by

one skilled in the art as referring to, at the very least, any of the techniques described in the immediately preceding background section for preparing gas containing agents. One skilled in the art would reasonably conclude, that a selected gas used in a known existing technique, especially one explicitly disclosed in the application itself, would yield an improved contrast enhancing agent of the invention, as envisioned by the applicant. The use of proteins, liposomes, microspheres, and crystals in a saccharide diluent were explicitly disclosed as such existing techniques. No additional information would be required for one skilled in the art to reach this conclusion.

I understand that the above statements were made with the knowledge that willful false statements and the like are punishable by fine and/or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that any such willful false statement may jeopardize the validity of the subject patent application or any patent resulting therefrom.

Executed this 16 day of April, 1999 at Torrance, California.

PAMELA HILPERT, M.D., Ph.D.